REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the following remarks. Claims 2-20, 27-43, 46-49, 52-55 and 58-61 are pending in the application, with claims 7-20, 33, 34, 38-43, 46-49, 52-55 and 58-61 standing withdrawn from consideration by the Examiner as allegedly being drawn to non-elected subject matter. Accordingly, claims 2-6, 27-32 and 35-37 are under substantive examination. Any remarks herein are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More particularly, the Examiner asserts that, "based upon the limited working examples in the specification, and the insufficient disclosure regarding the identity of the generic amino acids present in naturally occurring claudin, it would require undue experimentation for one of skill to predict which of the innumerable sequences encompassed by the instant claims would function as a cell adhesion modulating agent, without further guidance and direction from the specification."

Applicants respectfully traverse this rejection, for reasons previously made of record, and further in view of the comments herein.

Applicants' claimed invention is drawn, in pertinent part, to a cell adhesion modulating agent that comprises at least five consecutive amino acid residues of a claudin CAR sequence, said claudin CAR sequence being present in a naturally occurring claudin and having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues.

Applicants' claims are thus drawn to a clearly defined genus of claudin CAR sequences, a species of which must: (1) contain at least five consecutive residues of SEQ ID NO:1; (2) have a sequence present in a naturally occurring claudin CAR sequence; and (3) contain no more than 50 amino acid residues. Applicants respectfully submit that this claimed invention is indeed fully enabled by the specification as originally filed.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (*United States v. Telectronics, Inc.*, 857 F.d2 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). "A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive." (*United States v. Telectronics, Inc.*, 857 F.d2 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). "Enablement is not precluded by the necessity for some experimentation such as routine screening.." (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants have identified in the subject application a critical region of the claudin cell adhesion protein involved in modulating claudin-mediated cell adhesion. The present invention is thus based on the identification of previously unknown cell adhesion recognition (CAR) sequences present in claudin proteins (*e.g.*, page 14, lines 13-14). Applicants also disclosed in the specification as filed that a claudin CAR sequence according to the invention is one that is capable of modulating claudin-mediated cell adhesion and may be of any length, but preferably comprises 5-8 amino acids of a disclosed claudin CAR sequence (*e.g.*, page 16, line 28 to page 17, line 7). Applicants also disclosed, based upon analysis of this claudin CAR sequence, a conserved consensus sequence set forth in SEQ ID NO:1, and now currently claimed, shared by a multitude of naturally occurring claudin sequences (*e.g.*, page 17, line 18 to page 18, line 6). Further still, Applicants' specification indeed discloses numerous

representative, naturally occurring claudin CAR sequences according to the claimed invention, for example from mouse claudin-1 EC1 (WKIYSYAG; SEQ ID NO:34), mouse claudin-2 EC1 (WRTSSYVG; SEQ ID NO:42), human CPE-R WRVTAFIG; SEQ ID NO:50), mouse CPE-R (WRVTAFIG; SEQ ID NO:50), C. aethiops CPE-R (WRVTAFIG; SEQ ID NO:50), human RVP-1 (WRVSAFIG; SEQ ID NO:58), and rat RVP-1 (WRVSAFIG; SEQ ID NO:58), that conform to the concensus sequence set forth in SEQ ID NO:1 (*e.g.*, Table 1). Applicants also previously provided for the Examiner's convenience, in a Declaration under 37 C.F.R. § 1.132, confirmatory evidence that a peptide having a sequence comprising WKIYSYAG, and thus representing a claudin CAR sequence according to SEQ ID NO:1, is indeed capable of inhibiting the formation of tight junctions in epithelial cells, *i.e.,* is capable of modulating cell adhesion (Declaration filed May 13, 2002). Moreover, the specification as filed also offers detailed guidance, including numerous illustrative assays known to the skilled artisan, concerning the screening of a claimed peptide according to SEQ ID NO:1 for cell adhesion modulating activity (*e.g.*, page 39, line 26 to page 45, line 11).

Applicants respectfully submit that an artisan of ordinary skill, in view of the instant disclosure, could readily identify, make and use naturally occurring claudin CAR sequences according to the claimed invention, including claudin CAR sequences other than the numerous naturally occurring claudin CAR sequences specifically recited by the specification. Additional claudin proteins have and continue to be identified, many indeed containing a claudin CAR sequence according to Applicants' SEQ ID NO:1. For instance, a simple sequence search of publicly available databases using a claudin-1 CAR query sequence according to the instant disclosure readily identifies numerous naturally occurring claudin CAR sequences meeting the definition of Applicants' SEQ ID NO:1 (illustrative results shown below).

Illustrative Naturally Occurring Claudin CAR Sequences of SEQ ID NO:1

W-K/R-Aaa-Bbb-**S/A-Y/F**-Caa-**G (SEQ ID NO:1)**

WKIY**SY**AG	mouse claudin 1 (QUERY)
WKIY**SY**AG	rat claudin 1
WRIY**SY**AG	human claudin -1
WKQS**SY**AG	human claudin 19

WKQS**SY**AG	mouse claudin 19
WKMS**AY**VG	brare claudin-7
WRVT**AF**IG	human claudin-4bb
WKVT**AF**IG	brare claudin like protein ZF-A89
WKVT**AF**IG	human claudin-6
WRVT**AF**IG	cerae claudin-4
WRVT**AF**IG	mouse claudin-4
WRVS**AF**IG	rat claudin-3
WKVT**AF**IG	mouse claudin-6
WRVS**AF**IG	human claudin-3
WRVT**AF**IG	canfa claudin 3
WRVS**AF**IG	mouse claudin-3
WRVT**AF**IG	brare claudin-like protein ZF-A9
WKVT**AF**IG	human claudin-9
WRVS**AF**VG	human claudin-17
WKVT**AF**IG	mouse claudin-9
WRTS**SY**VG	mouse claudin-2
WRTS**SY**VG	canfa claudin-2
WKTS**SY**VG	human claudin-2

These naturally occurring claudin CAR sequences of SEQ ID NO:1 would be reasonably expected, based upon their sequence conservation in this critical binding region for claudin-mediated cell adhesion, to be capable of modulating cell adhesion based upon Applicants' specification as filed and further in view of what is well known in this art.

A patent applicant need not teach, and preferably omits, what is well known in the art. (*Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987), *cert. denied*;, 484 U.S. 954 (1987)).

It is well known in the art to which the claimed invention pertains that many cell adhesion molecules function on the basis of homophilic and heterophilic interactions with other cell adhesion molecules (*e.g.*, Background of Invention; page 1, line 13 to page 3, line 21). It is also well known in the art that for many of these cell adhesion molecules, the amino acid residues that are important for direct interaction with another cell adhesion molecule have been identified and characterized and minimal sequences important for activity have been defined. For instance, Applicants previously identified and characterized a region of the N-cadherin cell adhesion molecule involved in cadherin-mediated cell adhesion, just as they have done in the instant application for claudin, and defined a three amino acid HAV motif important in the modulation of cadherin-mediated cell adhesion (*see, e.g.*, U.S. Patent No. 6,031,072, issued

February 29, 2000). Similarly, Applicants have previously identified and characterized a region of the occludin cell adhesion molecule involved in occludin-mediated cell adhesion, just as they have done in the instant application for claudin, and defined a minimal four amino acid LYHY motif important in the modulation of occludin-mediated cell adhesion (*see, e.g.*, U.S. Patent No. 6,310,177, issued October 31, 2001). Further still, Applicants have previously identified and characterized a region of the β-catenin cell adhesion molecule involved in β-catenin-mediated cell adhesion, just as they have done in the instant application for claudin, and defined a minimal five amino acid KHAVV motif important in the modulation of β-catenin-mediated cell adhesion (*see, e.g.*, U.S. Patent No. 6,551,994, issued April 22, 2003).

Accordingly, Applicants' disclosure, coupled with the general level of knowledge and understanding in the art of cell adhesion proteins, provides the skilled artisan with a more than reasonable expectation that a five amino acid sequence of SEQ ID NO:1, as currently claimed, can be used as a cell modulating agent. Just as numerous other cell adhesion molecules known and described in the art possess CAR sequences of five (and often fewer) amino acid residues and retain an ability to modulate cell adhesion, so too would it be expected in view of Applicants' disclosure that a five consecutive amino acid sequence of the claudin CAR consensus sequence of SEQ ID NO:1 can be identified, made and used according to the claimed invention employing only routine and art-recognized materials and techniques, without any undue or unreasonable experimentation.

Reconsideration of the Examiner's rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

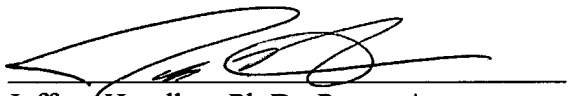
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Orest W. Blaschuk et al.

SEED Intellectual Property Law Group PLLC



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